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Theophylline–nicotinamide cocrystal formation in physical mixture during storage

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ABSTRACT

Pharmaceutically relevant properties, such as solubility and dissolution rate, of active pharmaceutical ingredients can be enhanced by cocrystal formation. Theophylline and nicotinamide are known to form cocrystals, for example if subjected to solid-state grinding. However, under appropriate conditions, cocrystals can also form in physical mixtures without any mechanical activation. The purpose of this work was to study whether theophylline and nicotinamide could form cocrystals spontaneously, without mechanical activation. Crystalline theophylline and nicotinamide powders were gently mixed manually in a 1:1 molar ratio and stored at different relative humidity and temperature conditions. The solid state of the samples was analyzed by differential scanning calorimetry, Raman spectroscopy and X-ray powder diffractometry. Three different variations of theophylline were used as starting materials, e.g., two size fractions of theophylline anhydrate (large 710 μm–1 mm and small 180–355 μm), and monohydrate (recrystallized from water). As a reference, anhydrous theophylline–nicotinamide cocrystals were prepared by solid-state grinding. The results of this study indicate that theophylline–nicotinamide cocrystals can form without any mechanical activation from physical mixtures of theophylline and nicotinamide during storage. For anhydrous samples, storage humidity was found to be a critical parameter for cocrystal formation. Increasing temperature was also found to have an accelerating effect on the transformation. The effect of particle size of anhydrous theophylline on the transformation rate could not be completely resolved; DSC and Raman indicated slightly faster transformation with a physical mixture prepared from large size fraction of anhydrous theophylline, but the differences were only minor. Cocrystal formation was also observed in the physical mixture prepared from theophylline monohydrate, but the rate was not as high as with samples prepared from anhydrous material.

1. Introduction

The solid form of an active pharmaceutical ingredient (API) may have a critical effect on the stability and processing properties of the material and even more important, on the performance of the drug when taken by the patient (Phadnis and Suryanarayanan, 1997; Tantry et al., 2007; Jung et al., 2010). Solid forms can be divided into the following categories: crystalline polymorphs, in which molecules have a specific long range arrangement (polymorphism refers to one chemical composition with different crystalline arrangements); amorphous, where no long-range arrangement of molecules is present; solvate, where solvent molecules (liquid at room temperature) are incorporated into the crystal lattice (if the solvent molecule is water, this form is called a hydrate); salt, which is a multi-component solid formed via proton transfer from an acid to a base; and finally, a cocrystal, which resembles solvates in the sense that they consist of two or more molecular entities, with the difference that in cocrystals both compounds are solid in ambient conditions and they exist in a stoichiometric ratio. If cocrystals are compared to salts, the difference is that no proton transfer occurs in cocrystal formation (Aakeröy et al., 2007). Although cocrystals have been known for some time, they are a poorly studied class from the view point of pharmaceuticals.

Screening and selecting a polymorphic form for a drug product is essentially finding the balance between good solubility (amorphous) and stability (crystalline). The advantage of cocrystals over single-component polymorphs is that not only stability but also solubility can be enhanced by formulating the API into a cocrystal form (Trask et al., 2006; Lu and Rohani, 2009). The salt form is also very often used, but acid–base pairing is not a possible

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option for all molecules, thus non-ionizable molecules are incapable of undergoing salt formation (Trask et al., 2006). The versatility of the cocrystal approach is the most obvious benefit, because the formation of cocrystals depends on the mutual recognition of the API and the cocrystal former (Friščić and Jones, 2010).

Cocrystals can be prepared by a variety of methods, for example dry grinding, solvent-drop grinding, slow evaporation from a solution, growth from the melt, and usually the obtained phase is not dependent on the synthetic methodology (Shan and Zaworotko, 2008). In addition cocrystals can prepared in several different ways, they can also be formed spontaneously under appropriate conditions (Maheshwari et al., 2009; Arora et al., 2011).

Theophylline is an API used for treatment of respiratory diseases, such as asthma. It has been reported to exist as four anhydrate polymorphs and as a monohydrate form (Seton et al., 2010). Nicotinamide is a member of the vitamin B family and it has been reported to exist as four polymorphs (Hino et al., 2001). Theophylline and nicotinamide are known to form a cocrystal, for example via solid-state grinding; this cocrystal has improved solubility properties as compared to pure theophylline powder (Lu and Rohani, 2009). However, as far as we are aware, it is not known if theophylline and nicotinamide can form a cocrystal without any mechanical activation.

In this study, physical mixtures of theophylline and nicotinamide were stored under different temperature and relative humidity (RH) conditions. The experiment was carried out for more than 250 days and the solid state of the samples was analyzed using three complementary techniques at specific time points during the experiment: thermal analysis by differential scanning calorimetry (DSC), lattice-level analysis by X-ray powder diffractometer (XRPD) and molecular-level analysis by Raman spectroscopy. A multivariate method, principal component analysis (PCA), was applied for the analysis and interpretation of Raman spectra.

2. Materials and methods

2.1. Raw materials and preparative methods

Nicotinamide (Form I) was purchased from Fluka Analytical (Steinheim, Germany) and anhydrous theophylline (Form II) from Sigma–Aldrich (Steinheim, Germany). The purity of both materials was >99%. Nicotinamide was used as received. With respect to theophylline, three different variants were prepared: monohydrate and two size fractions of anhydrate.

The size fractions were produced by sieving: pure anhydrate theophylline was placed on top of a test sieve set (Retsch, Haan, Germany) and was shaken with a sieve shaker (Retsch, Haan, Germany) at a frequency of 40 Hz for 5 min. The particle size of large particles selected for the study was 710 μm–1 mm and small particles 180–355 μm.

Theophylline monohydrate was recrystallized from water: purified water (Millipore Elix-5 UV, Progard 2, Millipore SAS, Molsheim, France) was heated up to 80 °C. After this temperature was reached, theophylline was added until the solution was saturated, mixing the solution all the time. The resulting solution was cooled in an ice bath and the recrystallized theophylline monohydrate was filtered from the solution with a Büchner funnel. Finally, excess water was evaporated from crystals in a fume hood at an ambient temperature for one day and the solid state was verified after evaporation with XRPD before the theophylline monohydrate–nicotinamide physical mixture was prepared. Due to hydration, the theophylline particles were found to form needle-shaped crystals, thus the particle size of theophylline monohydrate was not measured.

In the preparation of the physical mixtures, nicotinamide and the different forms of theophylline were weighed in a 1:1 molar ratio and gently mixed with a card in a mortar (no mechanical activation), respectively. Subsequently, Day 0 measurements were performed and after that the experiment was started by placing the mixtures at different relative humidity and temperature conditions as described in Table 1. All of the samples were placed and stored in 12-well plates so that one plate contained all of the samples of one storage condition. Hereafter the following abbreviations for the samples will be used: TA = theophylline anhydrate (non sieved); TAL = large particle fraction of anhydrous theophylline; TAS = small particle fraction of anhydrous theophylline; TM = theophylline monohydrate; Nt = nicotinamide; TAL–Nt = physical mixture of large particle fraction of anhydrous theophylline and nicotinamide; TAS–Nt = physical mixture of small particle fraction of anhydrous theophylline and nicotinamide; TM–Nt = physical mixture of theophylline monohydrate and nicotinamide.

The low humidity condition was achieved by placing silica gel in sealed containers. The humidity had been intended to be 0%, but when it was measured during the experiment, it was observed that such a low value was almost impossible to attain. However, the relative humidity control revealed the value to be <5% all the time during the experiment, which was considered as an acceptable level. The 75% relative humidity condition was prepared by using saturated NaCl solution (Greenspan, 1977). The containers were kept at two temperatures, 22 °C and 50 °C. Temperature and humidity conditions were monitored with Amprobe TH-1 relative humidity and temperature probe (Amprobe, Everett, WA, USA)

As a reference, TA–Nt cocrystals were prepared via solid-state grinding with a Retsch MM400 mixer mill: TA and Nt were weighed in a 1:1 molar ratio (TA 360.32 mg, Nt 244.24 mg), into the grinding jar (25 ml). Two steel balls (15 mm) were added to the jar which was then mixed for 15 min at a frequency of 20 Hz.

2.2. Analytical methods

The solid state of the samples was analyzed in an X-ray powder diffractometer (XRPD; Bruker D8 Discover, Bruker AXS, Inc., Madison, WI, USA) with a theta–theta setup, using Cu Kα radiation (λ = 1.54 Å, tube voltage 40 kV, tube current 40 mA). Each sample was scanned from 5° to 36° (2θ) with steps of 0.02° with a total scan time of 5 min 20 s. During the measurements, the samples were rotated at a speed of 30 rpm.

Raman spectra were collected with a Kaiser Raman RXN1 spectrometer equipped with a PhAT probe (Kaiser Optical Systems, Inc., Ann Arbor, MI, USA). Invictus laser source (Kaiser Optical Systems, Inc., Ann Arbor, MI, USA) was used at 785 nm with 400 mW power. The spectra were collected with an exposure time of 3 s and 2 accumulations. The spectral region from 250 to 1909 cm^{-1} was used in the data analysis. The PhAT probe was selected because its laser beam is optically expanded (up to 6 mm) providing a larger measurement area, but it also produces reduced thermal stress in the sample as compared to a conventional probe. All Raman measurements were performed in a closed box to prevent ambient room light from affecting the spectra.

Table 1
Temperature and humidity conditions used in the study.

Temperature (°C)	Relative humidity (%)
22	<5
22	75
50	<5
50	75